FDA Executive Summary

Prepared for the
***December 5, 2012** meeting of the*
Circulatory System Devices Panel

Classification of Intra-Aortic Balloon Pump (IABP) Devices
(21 CFR 870.3535)

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1 INTRODUCTION

On December 5, 2012, the Food and Drug Administration (FDA) will convene the Circulatory System Devices Advisory Committee to discuss the classification of Intra-Aortic Balloon Pump (IABP) devices (21 CFR 870.3535) for various intended uses. The IABP device is one of the remaining pre-amendment Class III medical devices currently cleared for marketing through the 510(k) pathway.

Industry responded to the Food and Drug Administration's (FDA) April 9, 2009 Federal Register (FR) Notice [Docket No. FDA-2009-M-0101] requesting safety and effectiveness information for IABP devices to determine whether the classification for the device should remain as Class III and require a premarket approval (PMA) application or be downclassified into Class I (General Controls) or Class II (Special Controls).

The panel will be asked to provide input on the risks to health and benefits of IABP devices. The panel will also weigh in on the FDA's proposed classification strategy for IABP devices including a split classification regulation to include both Class II (Special Controls) and Class III (PMA) classification based upon the available safety and effectiveness information. If the panel believes that Class II is appropriate for selected indications for IABP devices, the panel will also be asked to discuss appropriate special controls to mitigate the risks to health:

Reclassify (to Class II) IABP devices for **acute coronary syndrome cardiac and non-cardiac surgery**, and **complications of heart failure of both ischemic and non-ischemic etiologies**

Require PMAs (Maintain Class III) IABP devices for all other intended uses.

2 DEVICE DESCRIPTION

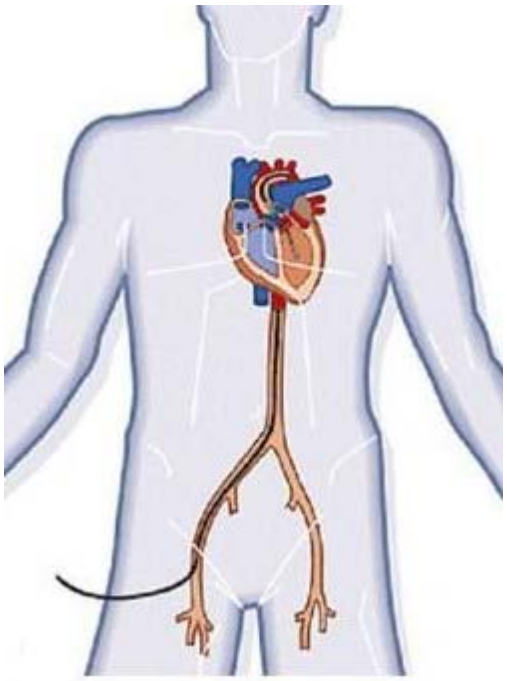
As currently defined in 21 CFR 870.3535

(a) Identification. An intra-aortic balloon and control system is a device that consists of an inflatable balloon, which is placed in the aorta to improve cardiovascular functioning during certain life-threatening emergencies, and a control system for regulating the inflation and deflation of the balloon. The control system, which monitors and is synchronized with the electrocardiogram, provides a means for setting the inflation and deflation of the balloon with the cardiac cycle.

The Intra-aortic balloon pump (IABP) system consists of the inflatable balloon and console which inflates in synchronization with the cardiac cycle. The balloon is usually manufactured from polyurethane. It is inserted through the femoral artery and resides in the descending aorta. Conventional timing sets inflation of the balloon to occur at the onset of diastole or the aortic valve closure timepoint. During diastole, the balloon will

inflate, increasing blood flow to the coronary arteries, therefore increasing myocardial oxygen supply. The balloon remains inflated throughout the diastolic phase, maintaining the increased pressure in the aorta. The deflation of the balloon takes place at the onset of systole during the isovolumetric contraction or very early in the systolic ejection phase. This deflation will cause a decrease in pressure in the aorta and this decrease in pressure assists the left ventricle by reducing the pressure that needs to be generated to achieve ejection through the aortic valve. As the balloon deflates during systole, it increases blood flow to the systemic circulation by reducing afterload and also decreases the oxygen demand of the myocardium.

Insertion site



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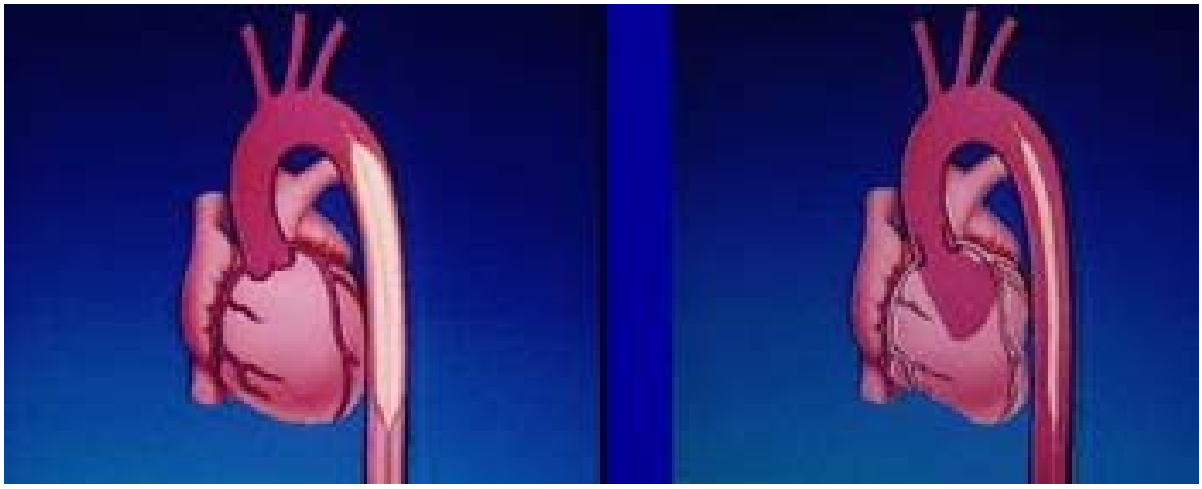

Diastole: inflation

Systole: deflation

Picture copied from http://www.rcisreview.com/cardiogenicshock.htm

Console

Picture copied from http://www.texasheart.org/research/images/iabp_console.jpg

The console provides the pneumatic flow of helium to the balloon so that it can inflate and deflate. This console includes software that controls the inflation and deflation of the balloon based upon the patient's ECG or arterial pressure waveform. The console also controls the amount of helium that is transferred from the internal helium cylinder to the balloon. Most balloons come in sizes of 30cc, 40cc, and 50cc with a catheter diameter of 7.5Fr or 8Fr. Helium is used as the gas because its low viscosity allows the gas to travel from the console through connecting tubes to the implanted balloon. It also has a lower risk of causing a harmful embolism should a leak or balloon rupture occur while the device is being used.

3 CLEARED INDICATIONS FOR USE

As noted previously, IABP devices are defined in the regulations under 21 CFR 870.3535; however, the identification does not currently include specific indications for this technology. The indications for use for the IABP device have evolved over the years. Initially, IABP was developed to provide circulatory support in established cardiac decompensation that was considered reversible such as failure to wean from cardiopulmonary bypass support following cardiac surgery. The limited intervention necessary for and the ease with which an IABP can be deployed have allowed its use to be extended beyond management of cardiac decompensation to providing prophylactic support for interventions associated with high cardiac risk and to provide relief from imbalances of coronary supply and metabolic demand. Employed to supplement an inadequacy of medical support of the failing circulation, the use of the IABP can obviate or delay the need for more invasive alternative mechanical circulatory support systems, e.g., ventricular assist devices, as a bridge to definitive treatment.

IABP devices are used in adult and pediatric populations. The balloon pump is intended for use in the health care facility setting.

The clinical use of IABP and the expansion of indications over the decades are listed

below:

1. Pre-Amendment (prior to May 28, 1976) – First reported clinical use of the IABP was in 1968. Indications included: Myocardial infarction (MI) leading to left heart failure and early signs of cardiogenic shock, and interim left ventricular support to permit the performance of emergency coronary artery bypass surgery (CABG).

2. 510(k)s cleared between 1980 and 1989 – Indications included: Refractory ventricular failure, cardiogenic shock, unstable refractory angina, impending infarction, mechanical complications due to acute myocardial infarction (i.e.. ventricular septal defect, mitral regurgitation or papillary muscle rupture), ischemia related intractable ventricular arrhythmias, cardiac support for high risk general surgical patients, and septic shock.

3. 510(k)s cleared between 1990 and 1999 – Same indications as in # 2 above with the addition of: weaning from cardiopulmonary bypass, support and stabilization during coronary angiography and angioplasty and intraoperative pulsatile flow generation.

4. 510(k)s cleared between 2000 and present – Same indications as in # 2 and # 3 above with the addition of: Prophylactic support in preparation for cardiac surgery, post-surgical myocardial dysfunction, cardiac contusion, mechanical bridge to other assist devices, cardiac support following correction of anatomical defects and support for failed angioplasty and valvuloplasty.

Section 7.1 will discuss the literature that has been systematically reviewed as part of our assessment of data that represents a reasonable assurance of safety and effectiveness for IABP. We have grouped the indications for use into several categories to facilitate summary of the published data and indications for which IABP devices have been cleared (e.g., acute coronary syndromes, cardiac and non-cardiac surgery, and heart failure of ischemic and non-ischemic etiologies, and other uses (e.g., septic shock and intra-operative pulsatile flow generation.)

4 CLASSIFICATION AND REGULATORY HISTORY FOR 21 CFR 870.3535

A brief summary of the regulatory history for IABP devices is provided below.

1976 Classification Panel Meeting, 1979 Proposed Rule and Classification Panel Recommendation, 1980 Final Rule

The classification of IABP devices was initially discussed at the Cardiovascular Device Classification Panel meeting on October 18, 1976 (41 FR 39818). The general function of the committee was to review and evaluate available data concerning the safety and effectiveness of devices currently in use and make recommendations on classification of these devices, including IABP devices.

On March 9, 1979, FDA published a proposed rule outlining the recommendations of the panel and proposed classification of IABP devices as Class III requiring premarket approval (44 FR 13369). The proposed rule provided the following in the "Summary of reasons for recommendation" :

- "The Panel recommends that the intra-aortic balloon and control system be classified into Class III because the device is life supporting and, because the Panel believes that there is insufficient medical and scientific information to establish a standard to assure the safety and effectiveness of the device."
- "Controversy exists as to whether the device is beneficial in many situations in which it is used, and that it is difficult to use the device safely and effectively."
- "Accurate and precise labeling and directions for use are especially critical. The Panel was "concerned that the various components of the device would not function properly if its modular components were poorly matched." "The balloon of the device is used within the main artery of the body and because this portion of the device in contact with internal tissues and blood, the materials used with it require special controls."
- "The device is electrically powered and portions of the device may be in direct contact with the heart, the electrical characteristics of the device, e.g., electrical leakage current, need to meet certain requirements."
- "If the design of the device is inadequate for accurate and precise blood pumping, a resulting failure could lead to death."
- The Panel based their recommendations on the potential hazards associated with the inherent properties of the device and on their personal knowledge and experience with the device.
- Risks to health identified by the Panel are discussed in Section 6.

No written comments were received regarding the proposed regulation to classify the IABP devices into Class III. As a result, the final rule was published on February 5, 1980 (45 FR 7939). The following codified language was published in Part 870 of the Code of Federal Regulations:

870.3535 Intra-aortic balloon and control system

(a) Identification. A intra-aortic balloon and control system is a device that consists of an inflatable balloon, which is placed in the aorta to improve cardiovascular functioning during certain life-threatening emergencies, and a control system for regulating the inflation and deflation of the balloon. The control system, which monitors and is synchronized with the electrocardiogram, provides a means for setting the inflation and deflation of the balloon with the cardiac cycle.

(b) Classification. **Class III (premarket approval)**

In 1987, FDA published a clarification by inserting language in the codified language stating that no effective date had been established for the requirement for premarket approval for IABP devices (52 FR 17736, May 11, 1987). FDA is obligated to issue a notice calling for PMAs and establishing the effective date of that requirement.

2009 515(i) order for Remaining Class III Pre-Amendments Devices

On April 9, 2009, FDA issued an order requiring the manufacturers of 25 of the 27 remaining Class III preamendments devices (including Intra- aortic balloon pump devices) to submit a summary of "…information known or otherwise available to them respecting such devices, including adverse safety or effectiveness information concerning the devices…in order to determine…whether the classification of the device should be revised to require the submission of a PMA or a notice of a completion of a Product Development Protocol (PDP), or whether the device should be reclassified into Class I or II." (74 FR 16214). Letters were sent to every IABP manufacturer registered and listed with FDA, notifying them of this request. This information was requested to be submitted by August 7, 2009.

5 INDUSTRY RESPONSE TO APRIL 9, 2009 515(i) ORDER

Four of the five manufacturers of IABP devices responded to FDA's call for information and provided the following information:

- Cleared Indications For Use (IFU);
- Device description;
- Device labeling;
- Summary of known and potential risks;
- Alternative therapies/practices;
- Summary of clinical and preclinical data; and
- Bibliography

These four manufacturers collectively hold a total of 91 (61%) of the 149 510(k) cleared IABP device products (balloon catheters and pumps) to date. One of the four manufacturers stated they are "not aware of adequate and valid scientific information that would support reclassification of the device to Class I or II." The remaining three manufacturers all recommend reclassification for all indications to Class II for the IABP devices.

Most responses included information in support of reclassifying IABP devices from Class III to Class II Special Controls. All of the supporting information is based on 1) Review of the clinical literature; 2) pre-clinical and clinical testing; 3) 40 or more years of information and knowledge about the clinical use of these devices; and 4) the overall volume of 510(k) cleared IABP device products.

The risks identified by the 4 manufacturers will be discussed in Section 6. The clinical data and bibliography provided will be reviewed in Section 7.

6 DISCUSSION OF RISKS TO HEALTH

The March 9, 1979 proposed rule (Docket No. 78N-1487) identified the following risks to health for IABP devices:

- Cardiac arrhythmias or electrical shock: Excessive electrical leakage current can disturb the normal electrophysiology of the heart, leading to the onset of cardiac arrhythmias.

- Ineffective cardiac assist: Failure to sense or synchronize on heartbeat or failure to inflate and deflate at the proper intervals can lead to improper or ineffective pumping of blood.

- Thromboembolism: Inadequate blood compatibility of the materials used in this device and inadequate surface finish and cleanliness can lead to potentially debilitating or fatal thromboemboli.

- Aortic rupture or dissection: Improper sizing or over inflation of the balloon can cause a rupture in the main artery.

- Limb ischemia: Improper operation of the device which restricts blood flow to the peripheral vascular tree results in tissue ischemia in the limbs.

- Gas embolism: Balloon rupture or a leak in the balloon can cause potentially debilitating or fatal gas emboli to escape into the bloodstream.

- Hemolysis: Poor material-blood compatibility or excessive disruption of the normal hemodynamic flow patterns can cause hemolysis.

FDA believes that these risks are still relevant for IABP devices. In considering additional risks to health, FDA evaluated likely device related adverse events reported in the FDA Manufacturer and User Facility Device Experience (MAUDE) database and/or identified by the manufacturers who responded to the 2009 call for information including the following:

- Infection
- Insertion site bleeding
- Leaks of the membrane or catheter
- Balloon entrapment
- Insertion difficulty/inability to insert the IAB
- Failure of the balloon to unwrap
- Malposition of the balloon in the patient
- Vessel occlusion resulting in infarction to an organ (including paraplegia)
- Thrombocytopenia

The panel will specifically be requested to comment on the risks to health identified and whether there are additional risks that should be considered for IABP devices and indications.

Current Contraindications for IABP use:

We also want to advise the panel that all IABP devices currently have the following contraindications as part of their labeling. These should be considered as part of the risks to health discussion as well as potential mitigations:

- Severe aortic insufficiency – as the balloon inflates, blood may be forced across the valve thereby overloading the ventricle and increasing cardiac work.
- Aortic aneurysm – the increased pressure generated by counterpulsation or trauma caused during IABP insertion may cause the aneurysm to rupture.
- Aortic Dissection – Insertion of the balloon and movement caused by inflation and deflation of the balloon may cause extension of the existing aortic dissection, or aortic rupture.
- Severe peripheral vascular disease of the aortoiliac and femoral arteries may limit the ability to advance the catheter through atherosclerotic vessels.
- Severe coagulopathy
- Sepsis

7 SUMMARY OF CLINICAL EVIDENCE

7.1 Literature Review

A systematic literature search of articles published after 1975 yielded 274 articles, of which 34 were identified during the initial epidemiological review for further qualitative synthesis. A supplemental literature review was subsequently conducted in September/October 2012 which yielded additional studies for consideration of IABP safety and effectiveness.

Most of the studies in the literature review examined multiple indications for use. Based on primary studies that examined specific indications for use, the most commonly studied indications for use were:

- Support of patients in cardiogenic shock (CS) in patients presenting with acute myocardial infarction (AMI)

- Support for diagnostic percutaneous revascularization and interventional procedures such as angioplasty or stent placement in diseases such as atherosclerotic coronary artery disease, facilitated by IABP placement

- Prophylactic support in preparation for cardiac surgery

- Post-surgical myocardial dysfunction/low cardiac output syndrome

- Support for complications from heart failure; and

- Mechanical bridge to other assist devices and cardiac support following correction of anatomical defects.

The Benchmark counterpulsation registry, an international IABP registry of Datascope IABP implantations published in 2003, enrolled 19,636 US and 3,027 EU patients.[1] It serves as a comprehensive platform by which to understand the usage of IABP as it is a prospective, international registry of patients who receive intra-aortic balloon pumps within participating institutions. Within the Benchmark registry, the most frequent indications for use of IABP were:

- provide hemodynamic support during or after cardiac catheterization (20.6%);
- cardiogenic shock (18.8%);
- weaning from cardiopulmonary bypass (16.1%);
- preoperative use in high risk patients undergoing angioplasty or coronary artery bypass grafting (13.0%); and
- refractory unstable angina (12.3%).

Device Safety (by Adverse Events)

IABP's and their use have evolved since they were first introduced in the 1960's. The devices have decreased in size significantly from 12Fr to current versions which are as small as 7Fr. In the earliest years, insertion was done surgically through a Dacron® graft sewn to the femoral artery. Beginning in 1979, percutaneous placement became possible. A few of the balloon pumps were placed through a trans-thoracic approach at the time of median sternotomy. As the device sizes decreased and more experience was gained using percutaneous approaches, complications related to the IABP have decreased considerably.[2]

The systematic literature review includes articles reviewed from 1975 to present, filtered in a systematic means for relevance, and is inclusive of adverse event rates observed in all patient subsets, device iterations and procedural placement techniques. For the purposes of this safety review, articles were considered for inclusion if they were published after 2000, constituting modern versions of the IABP in smaller diameters, placed percutaneously and reflective of currently cleared indications in the intended use populations. Event rates reflect this subset of the literature.

Mortality

Mortality rates in all studies involving IABP are high and reflect the significant mortality associated with the clinical scenarios of patients in whom IABP is used. These are patients with significant acute and chronic

comorbidities with high morbidity and mortality associated with their conditions, the therapeutics, and the procedures which they receive. In two studies which examined the Benchmark registry, which enrolled 16,909 and 22,663 patients, respectively, death was directly attributed to the IABP or IABP placement in <0.05% of patients[1,3].

Bleeding at Access Site

Six articles were found that reported the adverse event (AE) of bleeding at the access site.[3,4,5,6,7,8] The sample size for these studies ranged from 97-16,909. At <6 months, 0% and 4.3% of patients experienced bleeding at the access site (two studies). For the four studies in which no time was specified, the percentage of patients who experienced bleeding at the access site ranged from 0.6% to 26%. This AE ranged from 0.6% to 4.3% in studies with an adequate sample size. The outlier with access site bleeding of 26% was noted in a study with a small sample size and specifically studied patients presenting with acute MI with concomitant use of GPIIb/IIIa inhibitors.

Ruptured Aorta

Ruptured Aorta is a catastrophic complication that has been described in the literature. The systematic literature review of studies published after 2000 failed to reveal an incidence rate for this adverse event.

Femoral Artery Occlusion

Two articles were found that reported the AE of femoral artery occlusion[10,11] The sample size for these studies ranged from 135-181,599 patients and ranged in incidence from 0.1% to 3.0%. Neither study specified a time after insertion. 3.0% of patients experienced femoral artery occlusion in the smaller study of 135 patients. In the larger study, which was culled from patients captured in the National Cardiovascular Data Registry, the incidence of 0.1% is very low.

Groin Hematoma

One article reported the AE of groin hematoma.[12] The sample size for this study was 85, with an incidence of 2.4%.

Infection

Ten articles were found that reported the AE of infection.[13,3, 6,14,10,15,16,17,7,12,18] The sample size for these studies ranged from 22-19,543 In the timeframe of <6 months, the ranges were from 0 to 2.6% (two studies), from 6-12 months the percentage was 0.1% (one study), and beyond 12 months the range was 0.5 to 9.6% (four studies). In the four studies in which no time to event was

specified, the percentage of patients experiencing an infection ranged from 0.1 to 3.0%. The single study with a rate of infection of 9.6%, was a study of patients undergoing cardiac surgery who required IABP. These patients had severe comorbidities and of the 35% 30 day mortality, 9.6% died of sepsis.

Renal failure

Nine articles were found that reported the AE of renal failure.[19,20,21,5,6,22,23,16,12] The sample size for these studies ranged from 38-478. The highest percentage of patients with events was seen at <6 months, with a range of 1.2-17.6% (five studies). Beyond 12 months, the incidence noted in a single study was 2.8%. For the three studies in which no time to event was specified, the percentage of patients who experienced this AE ranged from 10.0 to 14.3%. Renal failure was reported in studies which examined patients with multiple indications for use, including support for diagnostic percutaneous revascularization and interventional procedures, prophylactic support in preparation for cardiac surgery, and post-surgical myocardial dysfunction/low cardiac output syndrome. This AE may represent the significant and severe patient comorbidities associated with IV dye use, hemodynamic compromise and other patient factors. A mechanism for IABP associated renal failure would include renal artery embolism or ischemia caused by restriction of renal blood flow as a result of the IABP. None of the studies claimed a direct relation between the IABP use and renal failure.

Hemorrhagic Stroke

Seven articles were found that reported the AE of hemorrhagic stroke.[21,4,5,22,23,7,24] The sample size for these studies ranged from 38-5495. The highest event rate was seen at >12 months, with an incidence of 9% (one study). For the one study in which no time to event was specified, there were no reports of stroke. For events reported at <6 months, the rates ranged from 0-2.6%. Because the IABP is placed in the descending aorta, rates for this adverse event are not likely directly device-related, but reflect the significant comorbidity associated with the patients in whom their clinical scenario warrants IABP insertion. Hemorrhagic stroke may have resulted from anticoagulant use necessitated by use of the IABP, but studies did not report whether the patients had other simultaneous indications for anticoagulant use independent of the IABP, or whether other agents such as anti-platelet medications may have contributed to the rates observed.

Other Adverse Events

Less frequently reported AEs included groin abscess/infection (3.7%), vascular complications – a composite of pseudoaneurysm, arteriovenous fistula, surgical repair, and limb ischemia (5.9-13.7% at <6 months),

amputation (0.1 – 1.5% ≥ 6 months) – and visceral thrombus (0.10% at 6-12 months).[25,5,14,26,7,27] There were no reports of phlebitis.

The safety data compiled from a selective literature review are presented below.

Safety Data from the literature review:
Ranges of Adverse Events among IABP users over Time

Adverse Event (range of sample sizes)	**No time specified**	**<6 months**	**6 - <12 months**	**≥12 months**
Device Related Mortality (16,909 - 22,663)	NR	.005%	NR	0.05 – 0.07%
Major limb ischemia/circulatory problem in leg (11 – 22,663)	0 - 5%	0 – 4.3%	0%	0.8-2.50%
Bleeding (35 – 22,663)	1.8 - 9%	0 – 20.6%	2 - 15%	7%
Bleeding at access site (97 - 16,909)	0.6 – 26%	0 - 4.30%	NR	NR
Rupture aorta/aortic injury (114)	NR	NR	NR	NR
Femoral artery occlusion (135-181,599)	0.1 - 3.0%	NR	NR	NR
Groin hematoma (85)	2.4%	NR	NR	NR
Infection (22 – 19,543)	0.1 – 3.0 %	0 - 2.6%	0.10%	0.5 – 9.6%
Renal failure (38 - 478)	10 -14.3%	1.2 - 17.6%	NR	2.8%
Hemorrhagic stroke (38 – 5495)	0%	0 - 2.6%	NR	7-9%
Vascular complications (51 – 114)	NR	5.9-13.7%	NR	NR
Pseudoaneurysm (85 – 181,599)	.4 - 1.2%	4.0%	NR	NR
Visceral thrombus (5,495)	NR	NR	0.1%	NR
Amputation (5,495)	NR	NR	0.1%	NR
Phlebitis (11-60)	0%	0%	NR	NR

NR – Not reported

A review of the Benchmark registry [3], which represents the single study with the largest enrollment and sample size, compiled the following complication rates:

<u>IABP complications and 30 Day In-hospital Mortality</u>

Study	n	Dates	Major Bleed	Major Limb Ischemia	Balloon-Associated Mortality	Hospital Mortality
Present study	16,909	1996–2000	0.8%	0.9%	0.05%	21.2%
Makhoul et al. (7)	436	1971–1985	1.1%	8.3%	0.5%	NR
Iverson et al. (13)	395	1973–1986	NR	10.9%	NR	47%
Gottlieb et al. (11)	206	1980–1982	NR	10%	0.5%	33%
Arafa et al. (25)	509	1980–1994	2.0%	7.5%	0.6%	49.1%
Alderman et al. (12)	106	1983–1986	NR	14.2%	0.9%	17.9%
Barnett et al. (8)	580	1983–1990	NR	11.9%	0.5%	44%
Eltchaninoff et al. (17)	231	1985–1990	3.5%	3.9%	0	NR
Busch et al. (26)	472	1985–1995	3.2%	27.5%	0.0%	28.3%
Funk et al. (15)	294*	1986–1987	NR	11.7%	NR	NR
Kvilekval et al. (22)	144	1986–1989	NR	10.4%	NR	17%
Miller et al. (16)	404†	1987–1989	NR	10%	NR	30%
Pi et al. (27)	129	1988–1992	14.7%‡	4.6%	NR	49.6%
Tartar et al. (20)	126	1988–1992	3.2%	12.2%‡	0	23.8%
Gol et al. (21)	493	1988–1993	5.1%	14%	2.6%	53.2%
Patel et al. (9)	691	1993–1995	3.5%	4%	0.4%	NR
Winters et al. (23)	870	1993–1996	6.9%	3.3%	0.2%	NR
Cohen et al. (10)	1119	1993–1997	4.6%	3.3%	0.4%	NR

*9 died acutely. †48 died acutely. ‡Combined major and minor. §30-day mortality.
IABP = intra-aortic balloon pump; NR = not reported.

Excerpt from Ferguson et al. 2001:p.1460. [65]

Clinical Safety Summary

In the Benchmark registry[1], there were low IABP complication rates, including IABP-related mortality (0.05% and 0.07% in the US and EU, respectively), major limb ischemia (0.09%, 0.8%) and severe bleeding (0.9%, 0.8%). This is consistent with other studies of IABP use with large sample sizes.

In the most recently published trial of IABP use, the IABP SHOCK II trial, published in October 2012 [24], 600 patients were randomized to IABP (301 patients) or no IABP (299 patients). The IABP group and the control group did not differ significantly with respect to the rates of adverse events, including major bleeding (3.3% and 4.4%, respectively; P = 0.51), peripheral ischemic complications (4.3% and 3.4%, P = 0.53), sepsis (15.7% and 20.5%, P = 0.15), and stroke (0.7% and 1.7%, P = 0.28). These rates represent recent IABP usage outcomes in a randomized trial of patients with high associated morbidity using modern aggressive interventional approaches to acute MI and cardiogenic shock which include the use of PCI and aggressive anticoagulation. The trial demonstrates low rates of adverse events which can be attributed directly to the IABP itself.

In conclusion, results from the literature review demonstrate low overall rates of complications. The patients in whom IABP is implanted have severe comorbidities and underlying illnesses. As a result, overall mortality in these patients is high. Patients recruited for studies on IABP are of a population segment that is at an inherently greater risk of mortality because of the high

risk procedures they require, and the illnesses that necessitated the procedures. It is difficult to discern whether the assessed mortality data relate to the device or the surgical procedures. The adverse events may be due to the device, the patients' anatomy, or the procedure. The literature does not always clearly specify which of these factors are directly associated with the event. The low number of deaths directly attributable to IABP suggests that IABP is a moderate risk therapeutic option in a high risk patient cohort. Additionally, there are trends to less balloon-related mortality over time, as balloon catheter sizes have decreased and procedural techniques have improved. The rates of individual adverse events related to IABP insertion are low-moderate, as detailed above. The specific AE's seen with larger ranges reflect either studies with low sample sizes, adverse events unable to be directly or mechanistically attributed to IABP, or are more appropriately reflective of the severe underlying comorbidies seen in these patient cohorts studied.

Device Effectiveness: (by Indication)
The device literature was systematically searched and device effectiveness was considered based on currently cleared indications. The FDA has grouped the indications into four broad categories, as noted below. Applicable literature is subsequently discussed regarding the available effectiveness information for each broad category.

1. **Acute coronary syndrome**
    - refractory unstable angina
    - impending infarction
    - post-infarction angina or threatening extension of myocardial infarction (MI)
    - complications of acute MI
    - support for diagnostic percutaneous revascularization and interventional procedures
    - ischemic related intractable ventricular arrhythmias
2. **Cardiac and non-cardiac surgery**
    - weaning from cardiopulmonary bypass (CPB)
    - cardiac support for non-cardiac surgery
    - prophylactic support in preparation for cardiac surgery
    - post-surgical myocardial dysfunction/low cardiac output syndrome
    - mechanical bridge to other assist devices
    - cardiac support following correction of anatomical defects
3. **Complications of heart failure of both ischemic and non-ischemic etiologies**
    - cardiogenic shock
    - refractory left ventricular failure
    - cardiac contusion with left ventricular dysfunction)
4. **All other intended uses**
    - septic shock

- intraoperative pulsatile flow generation

Acute Coronary Syndrome

The IABP Benchmark registry enrolled 5495 patients with acute myocardial infarction (AMI). [7] The most common indications for IABP use were AMI with cardiogenic shock (CS) (27.3%), hemodynamic support during diagnostic catheterization or PCI (27.2%) in AMI, IABP use before high-risk cardiac surgical intervention in AMI (11.2%), patients with mechanical MI complications (11.7%) and refractory unstable post-infarction angina (10%). The overall mortality rate in the IABP group in AMI patients was 20%; the mortality of patients with CS was 30.7%, which was low compared to other CS trials, and has been cited as evidence for a benefit from IABP use. Further evaluation of this registry has shown that in the US patients, compared to OUS patients, IABP was placed at earlier stages of the disease. After appropriate adjustment of risk factors, OUS patients show increased mortality (10.8% (US) vs. 18% (OUS), $P < 0.001$).

The results of the Global Utilization of Streptokinase and Tissue Plasminogen Activator (t-PA) for Occluded Coronary Arteries (GUSTO-1) trial [28] also demonstrated a 12-month survival advantage in CS with early IABP implantation. The significantly higher frequency of IABP use in the USA in relation to Europe in these two trials was associated with more bleeding complications, but also with a lower mortality rate.

The GUSTO-1 trial [28] was a retrospective study of IABP use in patients presenting with AMI and cardiogenic shock who received systemic fibrinolysis. Sixty-eight (68) of 310 CS patients received an IABP. Despite more adverse events in the early IABP group and more episodes of moderate bleeding, this cohort showed a trend toward lower mortality rates at 30 days (47%, 60%, P=0.11) and at 1 year (57%, 67%, P=0.04).

The National Registry of Myocardial Infarction (NRMI-2) published by Chen et al. [29] analyzed data from 12,730 patients in 750 US hospitals from 1994 to 1998 who were followed in the NRMI-2 registry. Hospitals were stratified into three groups by their annual number of IABP implantations as low, medium, and high-volume IABP centers. The median number of IABP placements was 3.4, 12.7, and 37.4 balloons per year, respectively, among these hospitals. Mortality rate due to an AMI with complicating CS decreased depending on the frequency of IABP placement (65.4% vs. 54.1% vs. 50.6%; $P < 0.001$). Multivariate analysis of patients with AMI and CS showed that hospitals with a high IABP placement rate reported lower mortality (OR = 0.71, 95% CI = 0.56 to 0.90),

Further analysis from the US NRMI-2 Registry by Barron et. al.[31] had also examined the effect of IABP in infarct-related cardiogenic shock (ICS)

patients. A total of 23,180 patients with ICS were identified, of whom 24% received systemic fibrinolysis (n = 5640) and 12.6% were treated by PTCA (n = 2925). The multivariate analysis showed that under these conditions, IABP treatment (38%, n = 7268) was associated with an 18% reduction in hospital mortality (OR = 0.82).

The thrombolysis and counterpulsation to improve survival in myocardial infarction complicated by hypotension and suspected cardiogenic shock or heart failure (TACTICS) trial [30] was a prospective randomized trial of IABP in patients with AMI treated with systemic fibrinolysis due to hypotension and suspected CS. The study was terminated early due to slow enrollment after 57 patients, 30 of whom received IABP. No significant difference in mortality was detectable in the overall population of patients at 30 days (27%, 33%, P=0.3) or at 6 months (34%, 43%, P=0.23), although non-significant trends toward improvement were seen. There was an observed mortality benefit seen in the subgroup of patients with Killip class III and IV, (39%, 80%, P=0.05). This was not the primary endpoint of this trial, and so must be considered with caution.

Waksman et al.[32] reported the outcomes of patients presenting with acute MI and cardiogenic shock treated by fibrinolysis. In-hospital survival in the 24 patients with cardiogenic shock treated with IABP was improved compared to 21 similar patients not given IABP (46% vs. 19%, P = 0.001). Although there was a high rate of revascularization in the former group, they had survival rates similar to historical control subjects (n = 35) who did not undergo revascularization (46% vs. 45%).

The Should We Emergently Revascularize Occluded Coronaries for Cardiogenic Shock? Registry (SHOCK) [33] included 251 patients presenting with AMI complicated by cardiogenic shock between January 1992 and April 1993. In patients treated with IABP, survival was 43% compared with 28% without IABP (n=173, P = 0.039). However, patients with IABP were significantly younger (64.5±10.7 versus 68.2±12.4 years, P = 0.039) and more often underwent cardiac catheterization (88% with IABP versus 30% without IABP, P < 0.0001). After adjusting for cardiac catheterization status, there was no significant association between mortality and IABP (P = 0.660). Among 47 patients who underwent PTCA, mortality rates did not differ by IABP use (62% with IABP versus 54% without IABP, P = 0.743). The success rates of PTCA were also similar for patients with and without IABP (69% versus 60%, P = 0.707).

Table 1. ***Effect of IABP in Clinical Trials***

	30-day mortality	6-month mortality	6-month mortality	6-month mortality	1-year mortality	Hospital mortality	Overall mortality
	All pts	All pts	Killip I/II	Killip III/IV			
TACTICS trial—Comparison of the 30-day and 6-month mortality of patients treated of systemic fibrinolysis in combination with or without IABP (16)							
	$P = 0.3$	$P = 0.23$	$P = 0.23$	$P = 0.05$	N/A	N/A	N/A
Fibrinolysis + IABP	M: 27% ($n = 33$)	M: 34% ($n = 33$)	M: 27% ($n = 14$)	M: 39% ($n = 18$)	N/A	N/A	N/A
Fibrinolysis − IABP	M: 33% ($n = 27$)	M: 43% ($n = 27$)	M: 8.6% ($n = 12$)	M: 80% ($n = 13$)	N/A	N/A	N/A
GUSTO trial—Comparison of the hospital, 30-day, and 12-month mortality of patients having a systemic fibrinolysis with or without additional IABP patients (14).							
	$P = 0.06$, adj. $P = 0.11$	P = ns	N/A	N/A	N/A	$P = 0.12$	N/A
Fibrinolysis + IABP	M: 47% ($n = 62$)	M: 57% ($n = 62$)	N/A	N/A	N/A	M: 48% ($n = 62$)	N/A
Fibrinolysis − IABP	M: 60% ($n = 248$)	M: 67% ($n = 248$)	N/A	N/A	N/A	M: 59% ($n = 248$)	N/A
NRMI-registry—comparison of hospital survival with systemic fibrinolysis with or without additional IABP support in ICS patients (17). OR for IABP 0.82 (0.72–0.93) $P < 0.01$							
Fibrinolysis + IABP	N/A	N/A	N/A	N/A	N/A	M: 48.7	N/A
Fibrinolysis − IABP	N/A	N/A	N/A	N/A	N/A	M: 66.9%	N/A
Effect of intra-aortic balloon counterpulsation (IABP) on mortality in patients with ICS and systemic fibrinolysis (18)							
IABP	N/A	N/A	N/A	N/A	M: 62%	M: 54%	N/A
IABP 20/24 (83%)							
Revasc 16/24 (67%)							
no IABP	N/A	N/A	N/A	N/A	M: 90%	M: 81%	N/A
IABP 0/21 (0%)							
Revasc 1/21 (67%)							
Influence of intra-aortic balloon pulsation (IABP) on mortality in patients with infarct-related cardiogenic shock and PCI treatment (17). OR (IABP) 1.27 (1.07–1.50) M: 90%							
PCI + IABP	N/A	N/A	N/A	N/A	N/A	N/A	47% (956/2035)
PCI + no IABP	N/A	N/A	N/A	N/A	N/A	N/A	41.9% (401/956)

M, mortality; PCI, percutaneous coronary intervention; Revasc., revascularization with percutaneous coronary intervention or coronary artery bypass surgery; ns, not significant; N/A, not available.

From M. Buerke et al. [34]

The IABP SHOCK Trial [35] randomized 45 consecutive patients from March 2003 to June 2004 presenting with AMI and CS undergoing PCI to IABP (19) or no IABP (21). Neither the primary endpoint (serial APACHE-II scoring during the first 4 days) nor the 28-day mortality (IABP: 36.8% [11/19], no IABP: 28.6% [6/21]) were significantly different. The authors concluded "In this randomized trial addressing addition of IABP in CS patients, mechanical support was associated only with modest effects on reduction of APACHE II score as a marker of severity of disease, improvement of cardiac index, reduction of inflammatory state, or reduction of BNP biomarker status compared with medical therapy alone." The study did demonstrate

improvement in hemodynamics, but it did not demonstrate a decrease in morbidity or mortality. The study is limited by its small sample size.

The IABP SHOCK II [36] Trial published October 4, 2012 randomized 600 patients presenting with AMI and CS to IABP (301 patients) or no IABP (299 patients). Two hundred seventy-seven (277) patients underwent early revascularization. At 30 days, 119 patients in the IABP group (39.7%) and 123 patients in the control group (41.3%) had died (relative risk with IABP, 0.96; 95% confidence interval, 0.79 to 1.17; P = 0.69). There were no significant differences in secondary endpoints or in process-of-care measures, including the time to hemodynamic stabilization, the length of stay in the intensive care unit, serum lactate levels, the dose and duration of catecholamine therapy, and renal function. The rates of adverse events were not significantly different between the groups. It is notable that 37 patients (13.4%) had the balloon pump inserted before revascularization and 240 patients (86.6%) had the balloon pump inserted after revascularization, which may affect effectiveness. There was no significant difference in mortality between the two groups (mortality, 36.4% and 36.8%, respectively; P = 0.96), but the differences in timing of treatment cannot be separated from demographics or comorbidities which may have led to differences in the timing of treatment between these two groups, confounding the results, making them difficult to interpret.

In summary, early studies of IABP demonstrated improved hemodynamics, supporting the purported mechanism by which IABP would improve outcomes in ischemia. In early data from trials of AMI complicated by cardiogenic shock treated with fibrinolysis, IABP treatment demonstrated improvement in mortality. In more recent trials of this patient population treated by early revascularization using PCI, as opposed to fibrinolysis, IABP treatment may have a reduced benefit. Trials performed to investigate the benefit of IABP using the modern standard of care have been underpowered to demonstrate improvement, or have had other limitations, such as variability in the timing of IABP usage.

Cardiac and non-cardiac surgery

Postcardiotomy low cardiac output syndrome (LCOS) has been seen in 2-9% of patients undergoing open-heart surgery, and is related to increased hospital mortality, morbidity, and costs. Multiple studies have looked at strategies to prevent this prospectively with prophylactic IABP placement, and also use of the IABP in weaning or supporting failing patients. Results of trials investigating the prophylactic IABP use in CABG to prevent LCOS have shown conflicting data.

Christenson et al. [37] randomized 30 high risk off-pump CABG surgery recipients to receive IABP preoperatively or no IABP. The use of IABP

improved preoperative and postoperative cardiac performance significantly ($P < 0.0001$). The post-op course was also improved, including decreased pneumonia and acute renal failure, shorter duration of ventilator support, and fewer patients requiring postoperative inotropic medications for greater than 48 hours. The lengths of stay in the intensive care unit (ICU) and in the hospital were shorter in the IABP group. This study demonstrated indices indicating efficient hemodynamic support during the surgery, a reduction in the risk of hemodynamic instability, and shorter lengths of stay in both the hospital and the ICU.

Miceli et al. [22] studied 141 consecutive patients from 2004-2007 undergoing CABG. Thirty-eight patients (27%) received prophylactic IABP. After risk-adjusting for propensity score, prophylactic IABP patients had a lower incidence of postcardiotomy low cardiac output syndrome (LCOS) (adjusted OR 0.07, $P < 0.006$) and postoperative myocardial infarction (adjusted OR 0.04, $P < 0.04$), as well as a shorter length of hospital stay (10.4 ± 0.8 vs. 12.2 ± 0.6 days, $P < 0.0001$) compared to those who did not receive IABP. This study showed that prophylactic IABP treatment for hemodynamically stable high-risk patients undergoing CABG may improve postoperative course, reducing postcardiotomy LCOS, postoperative myocardial infarction and length of hospital stay.

Other studies have demonstrated no benefit. Baskett et al. [38] reported no evidence of benefit of preoperative IABP insertion, with higher in-hospital mortality with the use of IABP. These results may be due to a very high proportion of urgent operations. Holman et al. [39] excluded patients receiving preoperative IABP for hemodynamic instability, recent myocardial infarction within 3 days of CABG and those undergoing emergent operations. They did not find any survival advantage for patients who received a prophylactic IABP insertion compared to risk matched control patients showing only a shorter post-CABG length of hospital stay.

A meta-analysis by Field et. al. [40] of 5 randomized clinical trials included 105 patients treated prophylactically with IABP, with 88 control patients. The authors concluded that available evidence suggests the preoperative intra-aortic balloon pump may have a beneficial effect on mortality and morbidity in specific high risk patient groups undergoing coronary artery bypass grafting; however, the randomized evidence is from a number of small trials, with a high proportion of unstable patients recruited at a single institution.

When considering patients with high cardiac risk undergoing non-cardiac surgery, the AHA/ACC 2009 [41] Guidelines on Pre-operative management of cardiac patients assessed the literature as such:

> "Several case reports have documented its use in patients with unstable coronary syndromes or severe CAD who are undergoing urgent

noncardiac surgery. Although the rate of cardiac complications is low compared with other series of patients at similarly high risk, there are no randomized trials to assess its true effectiveness."

Siu et al. [42] reported a single center experience with 8 patients with unstable coronary syndromes or severe coronary artery disease who underwent urgent noncardiac surgery. None of the patients suffered perioperative MI while the IABP was in place. Another case series by Grotz and Yeston [43] reported an additional 3 patients treated prophylactically with IABP with good results.

Another indication related to cardiac and non-cardiac surgery is IABP use as a bridge to other assist devices or transplantation. Norkiene et al. [44] studied 11 adult patients with decompensated dilated cardiomyopathy (CMP) listed for heart transplant who were recorded in the Benchmark Registry from Sept 2004-Dec 2005, with NYHA Class IV functional status. Frequency of complications and clinical outcomes were assessed prior to and after IABP insertion as well as hemodynamics and end-organ function (renal and hepatic). After 48 hours of intra-aortic balloon pump support, there was a significant increase of mean systemic arterial pressure from 74.5±9.6 to 82.3±4.7 mmHg (P = 0.02), and ejection fraction from 14.7±6.4 to 21.0±8.6 (P = 0.014). Improvement of the cardiac index, pulmonary wedge pressure and end-organ perfusion markers did not reach statistical significance. The authors concluded that intra-aortic balloon pump support may be successfully and safely used in the acute decompensated dilated cardiomyopathy patients as an urgent measure of cardiac support to stabilize the patient and maintain organ perfusion until transplant is available, ventricular assist device (VAD) is placed, or the patient is weaned from IABP.

In summary, the literature regarding the effectiveness of IABP in cardiac and non-cardiac surgery is conflicting, with some studies demonstrating utility and others which are equivocal or fail to demonstrate effectiveness. Demonstrating utility represents a challenge of clinical trial design, with well executed trials, free of crossover and bias, with carefully chosen patient selection criteria and endpoints. Given the benefit demonstrated in some such trials, it is clear that certain groups of patients with specific clinical indicators and features of surgical risk may benefit from IABP use for this group of indications.

Complications of heart failure

The IABP was the first mechanical treatment available for congestive heart failure. Prior to its introduction in 1968, the only available therapies were positive inotropic agents, vasopressors, and diuretics. Studies in animals and humans had demonstrated the hemodynamics signature of the device, with reduced afterload, decreased cardiac work, and increased myocardial perfusion. Intravascular monitoring during IABP use had demonstrated

increased mean arterial pressure (MAP), increased cardiac output and decreased pulmonary capillary wedge pressure (PCWP). Kantrowitz et al.[45] published the first clinical data of IABP therapy in patients with cardiogenic shock in 1968. He reported on two patients with cardiogenic shock who after IABP, inserted by arterial cut-down, manifested improved systemic arterial and central venous pressures, and increased urine output. In 1980, Bregman [46] described percutaneous insertion, which increased safety. The series published by Norkiene et al. [44], detailed above, documents the hemodynamic effects observed in a target population with dilated cardiomyopathy awaiting transplant, an analogous population and device indication.

Rosenbaum et al. [47] studied 43 patients with end stage CHF in whom IABP was used as a bridge to transplant. Twenty-seven (27) patients had non-ischemic CMP (NICM), and 16 had ischemic CMP (ISCM). Hemodynamics improved in both groups, immediately (15 to 30 min) following IABP insertion, with greater improvement ($p < 0.05$) in cardiac index and a trend toward greater reduction in filling pressures in the NICM group. Systemic vascular resistance fell to a similar degree in both groups. During continued IABP support (0.13 to 38 days in NICM, 1 to 54 days in ISCM), all hemodynamic changes persisted in both groups, with a larger decrease ($p < 0.05$) in systemic vascular resistance and greater increase ($p < 0.05$) in cardiac index in the patients with NICM. The reduction in filling pressures, however, tended to be greater in patients with ISCM. Complications from the IABP were low. The authors concluded that IABP use was both safe and effective in this group as a bridge to transplant.

In summary, most of the larger randomized studies demonstrating survival benefit in cardiogenic shock come in patients with cardiogenic shock from acute MI, as detailed above. There are data in smaller series of patients in heart failure, including indications such as bridge to transplant, children awaiting transplant, and acute decompensated dilated cardiomyopathy. Given the device's mechanism of action, the measured hemodynamic benefits, and the known safety profile, the device has been used ubiquitously over the last fifty years to support cardiac mechanics and hemodynamics in physiologic states consistent with the IABP's mechanism of action, while the heart recovers, or the patient is optimized for the next therapeutic treatment Clinical practice and expert consensus has followed from this evolution of the device use, and it is accepted as effective based on this background and the prolonged history of use. It is considered to be one therapeutic intervention among many used in a multifactorial approach to hemodynamic support in these sick patients.

Proposed Class III Indications (premarket approval): Safety and Effectiveness Data

IABP is currently cleared for two additional indications, Septic Shock and Intraoperative Pulsatile Flow Generation (IPFG), which we consider to be outside of the scope of the three categories of indications identified above. Based upon the lack of valid scientific evidence to demonstrate a reasonable assurance of safety and effectiveness for indications outside of those identified immediately above, FDA is recommending that all other indications, including septic shock and IPFG, should remain as Class III.

The Panel will specifically be requested to comment on whether there is sufficient safety and effectiveness data to support these indications.

Septic Shock

No articles regarding the safety or effectiveness of IABP for septic shock in humans were found through the systematic search. Therefore, the safety and effectiveness of IABP for septic shock in humans cannot be systematically determined from the published literature. The hemodynamic effects generated by IABP use do not address the fundamental hemodynamic derangements of the septic shock syndrome. The device has no theoretical or literature demonstrated utility in this clinical syndrome.

Intraoperative Pulsatile Flow Generation (IPFG)

The use of IABP for Intraoperative Pulsatile Flow Generation (IPFG) within all indications for use (IFU) ranges from <1% (1996 – 2001) to 42% (1971-1985). Within the entire Benchmark Registry[1], <1% to <4.2% of the IFUs were in the composite category of "Not indicated; miscellaneous, other (intraoperative pulsatile flow)." The limited literature regarding the safety and effectiveness of IABP for IPFG reflects the limited use of the device for this indication.

It is noted that the rate of 42% for IABP use in IPFG may be the highest reported rate for several reasons. First, this rate was reported from a single site study as opposed to the Benchmark Registry which is composed of 250 sites. Second, the rate was reported between January 1971 and July 1985, a decade before the Benchmark registry was initiated. Third, the article that reported 42% usage for this indication uses the phrase "intraoperative pump failure" without explanation. Within the literature review, it was assumed IABP use for "intraoperative pump failure" indicated that the IABP was used to compensate for this failure, thereby generating an intraoperative pulsatile flow. Alternatively, if "intraoperative pump failure" does not equate to IPFG, then the true proportion of IABP for IPFG in this timeframe is inflated within the review. This might account for the vast difference in IPFG use between this study and the Benchmark articles and may actually reflect a difference in terminology with the term IPFG referring to the hemodynamic mechanism of action of the IABP rather than a desire to specifically generate pulsatile flow,

as compared to continuous flow.

The IABP-related mortality and adverse events rates are low; however, these rates were not solely assessed within IPFG patients. Therefore, there is no published data regarding the mortality and adverse events rates in patients with IABP for IPFG. Given the limited use of IPFG (low sample size), any reports of adverse events would primarily be descriptive and hypothesis generating.

IABP use for IPFG, therefore, makes up a small percentage of the overall use of IABP within the past two decades. This may account for the limited publications regarding this indication. Three observational articles including two with data from the Benchmark Registry provided no conclusive evidence for safety or effectiveness for IPFG use. All three articles [1,3,2] state that the device is associated with low mortality and low adverse event rates. However, since no article stratified mortality by indication, these results do not apply specifically to IPFG. With the development and increased use of continuous flow VADs, comparative studies have failed to observe a difference in hemodynamic surrogates[48, 49], clinical outcomes[50] or neurocognition [51] with the use of pulsatile flow compared to continuous flow. This is directly applicable to the IABP indication of IPFG. All other mechanistic and hemodynamic effects of the IABP, with the exception of the pulsatility, have demonstrated effectiveness and are captured under the indications listed above to be proposed for reclassification into Class II.

Conclusion

While the literature may at times be equivocal, FDA contends that sufficient data has been provided to demonstrate a reasonable assurance of safety and effectiveness of IABP for the indications encompassed by Acute Coronary Syndrome, Cardiac and Non-Cardiac Surgery, and Complications of Heart Failure. There is currently no evidence from the published literature that IABP for septic shock and IPFG are both safe and effective.

7.2 MDR Report

The FDA/CDRH Division of Postmarket Surveillance conducted an search of the Manufacturer and User Facility Device Experience (MAUDE) database to identify the reported adverse events (AEs) for IABP. Due to the extensive time period the device has been on the market and the amount of data available, the MDR review period was limited to the last 10 years. The table below is a summary of the MDRs and device recalls for the DSP procode from January 1, 2002 to November 1, 2012. There were a total of 5493 events reported with IABP devices over a 10-year period. Based on a review of the literature [1], a reported 170,000 IABPs are placed each year internationally, approximately 75,000 being placed in the United States. Averaging the data over the10-year period, there are 19 deaths, 180 injuries, and 345

malfunctions per year. Although this data indicates a number of significant AEs, including death, there are several critical factors to consider as part of a benefit/risk assessment. Specifically, it should be noted that the intended population is a group of patients with high morbidity. The number of deaths and injuries is not necessarily reflective of the device itself but the very sick population in whom it is used.

The top reported device malfunctions were balloon leak, balloon rupture, and air leak. In most instances, if a balloon leaks or ruptures or there is a tubing air leak, the old balloon pump catheter is replaced with a new one.

Intra-aortic Balloon Pump (IABP) 21 CFR 870.3535 Class III device

Event Type Counts (MDRs) Procode: DSP												
	2002	**2003**	**2004**	**2005**	**2006**	**2007**	**2008**	**2009**	**2010**	**2011**	**2012**	Sum:
DEATH	9	5	12	16	18	17	14	15	31	30	22	189
INJURY	262	217	222	230	307	291	95	35	59	48	31	1797
INVALID DATA	5	1	1		4	3	4	5	4	6	2	35
MALFUNCTION	130	100	106	130	158	147	502	599	925	467	185	3449
OTHER	1	4	4	6	2	2	2	1		1		23
Sum:	407	327	345	382	489	460	617	655	1019	552	240	5493

IABP Device Recall History

The recall classification assigned by FDA indicates the relative degree of risk to public health of the product being recalled or considered for recall. There were a total of two Class I recalls and four Class II recalls for this device type during the last 10 years, as noted in the table below.

Recalls											
	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012
Class I +	0	0	0	0	0	0	0	1	1	0	0
Class II ++	0	0	0	0	0	0	2	1	1	0	0
Class III	0	0	0	0	0	0	0	0	0	0	0

+ Class I recall- There is a reasonable probability that the use of, or exposure to, a violative product will cause serious adverse health consequences or death.
++ Class II recall- The use of, or exposure to a violative product is not likely to cause

adverse health consequences.

The Class I Recalls involved one manufacturer and occurred in 2009 (1) and 2010 (1). The event in 2009 involved a fault in the connector of the pump tubing assembly. The event in 2010 involved the IAB catheter becoming stuck in the sheath causing a delay in therapy, bleeding or arterial injury. The correction for both events was return and replacement of the affected products.

The Class II Recalls involved two manufactures and occurred in 2008 (2), 2009 (1) and 2010 (1), as described below.

- 2008 – a leak in the helium drive system and a defective circuit board that caused the pump to exhibit intermittent malfunctions such as failure to start-up or reset of the display screen during therapy. The correction of both events was replacement of the defective part.
- 2009 – a non-functioning cable. The correction of the event was replacement of the cable.
- 2010 – console display related issues causing the user to be unable to view the IABP on the information screen. The correction of the event was manufacturer field service visits to affected units.

As noted above, approximately 75,000 IABP systems are used each year in the United States. The number of device recalls per number of devices used is relatively small. As such, IABP system manufactures appear to have a low incidence of manufacturing related defects.

7.3 Summary

Based upon the safety and effectiveness information provided by the manufacturers of the intra-aortic balloon catheter and control systems, MDR data and literature search, and expert consensus practice guidelines, FDA believes there is sufficient clinical evidence and non-clinical testing parameters to demonstrate a reasonable assurance of safety and effectiveness for a subset of the currently cleared indications for IABP devices. As noted above, for the proposed indications, FDA contends that the risks to health can be appropriately mitigated through the utilization of appropriate special controls as suggested below and the use of IABP devices for acute coronary syndrome, cardiac and non-cardiac surgery, complications of heart failure of both ischemic and non-ischemic etiologies should be reclassified into Class II.

Because there is a lack of safety and effectiveness data to support two specific indications, septic shock and intraoperative pulsatile flow generation, FDA seeks concurrence from the Panel that it is most appropriate to confirm that these indications should remain as Class III and we should proceed with a call for PMAs.

The Industry responses state the scientific literature shows the use of IABP devices has been well documented and the risks and complications associated with use of the device

are well known. Industry responses agree that understanding the risk/benefit relationship of the IABP allows proactive management of patients who may need the device to provide effective therapy while reducing the inherent risks associated with use of the device.

The literature has shown that this type of therapy is safe and effective in the intended patient population, for the indications proposed in Section 1. The complication rate and device failure rate is acceptable given the overall risk of mortality and adverse outcomes in the acute and sub-acute heart failure and acute coronary syndrome patient populations. The information provided by Industry supports the conclusion that the probable benefits to health from using the device for its intended uses and conditions outweigh the risks. FDA is confident that the current indications (not including the septic shock and intraoperative pulsatile flow generation) are appropriate and supported by the known physiology of the device's action as well as the published literature. The FDA literature search performed by the Division of Epidemiology and the Division of Cardiovascular Devices revealed septic shock to have no history of use, while intraoperative pulsatile flow generation was shown to have minimal use of unsubstantiated benefit or utility. As a result, there is a lack of data to support the safety and effectiveness of IABP devices for these indications. Consequently, the risks associated with the use of IABP for septic shock and intraoperative pulsatile flow generation cannot be mitigated using general and special controls and therefore should be regulated as Class III.

8 FDA RECOMMENDATION

For the purposes of classification, FDA considers the following items, among other relevant factors, as outlined in 21 CFR 860.7(b):

1. The persons for whose use the device is represented or intended;

2. The conditions of use for the device, conditions of use prescribed, recommended, or suggested in the labeling or advertising of the device, and other intended conditions of use;

3. The probable benefit to health from the use of the device weighed against any probable injury or illness from such use; and

4. The reliability of the device.

Part (g)(1) of this regulation further states "is the responsibility of each manufacturer and importer of a device to assure that adequate, valid scientific evidence exists, and to furnish such evidence to the Food and Drug Administration to provide reasonable assurance that the device is safe and effective for its intended uses and conditions of use. The failure of a manufacturer or importer of a device to present to the Food and Drug Administration adequate, valid scientific evidence showing that there is reasonable assurance of the safety and effectiveness of the device, if regulated by general controls

alone, or by general controls and performance standards, may support a determination that the device be classified into class III."

Special Controls

FDA believes that special controls, in addition to general controls, can be established to mitigate the identified risks and provide reasonable assurance of the safety and effectiveness of IABP devices when indicated for acute coronary syndrome, cardiac and non-cardiac surgery, and complications of heart failure of both ischemic and non-ischemic etiologies. As mentioned in Section 6, FDA concurs that the risks to health identified by the original classification panel still remain relevant for IABPs. In addition, other complications captured in the MAUDE database and provided by manufactures are included in the table below along with recommended mitigation measures for each risk in Table 1.

Table 1: Risk/Mitigation Recommendations for IABP Devices

Identified Risk	**Recommended Mitigation Measures**
Cardiac arrhythmias	Non-clinical performance evaluation Labeling
Ineffective cardiac assistance (Poor augmentation)	Non-clinical performance evaluation Labeling
Thromboembolism	Biocompatibility Sterility and Shelf Life
Aortic rupture or dissection	Labeling
Limb ischemia	Labeling
Gas embolism	Non-clinical performance evaluation Labeling
Hemolysis	Biocompatibility Labeling
Infection	Sterility and Shelf Life Labeling
Insertion site bleeding	Labeling
Leaks of the membrane or catheter	Labeling Non-clinical performance evaluation
Balloon Entrapment	Labeling

	Non-clinical performance evaluation
Insertion difficulty/Inability to insert the IAB	Labeling Non-clinical performance evaluation
Failure of the balloon to unwrap	Labeling Non-clinical performance evaluation
Malposition of the balloon in the patient	Labeling
Vessel occlusion resulting in infarction to an organ (including paraplegia)	Labeling Non-clinical performance evaluation
Thrombocytopenia	Labeling Non-clinical performance evaluation
Software malfunction	Software Verification, Validation and Hazard Analysis

When evaluating the adequacy of the proposed special controls below, it is important to understand that the FDA correlates the ability of each special control identified to mitigate an identified risk to health. Based on the proposed mitigation measures, FDA believes that the following special controls, in conjunction with general controls, would provide a reasonable assurance of safety and effectiveness of IABP device when specifically indicated for acute coronary syndrome; cardiac and non-cardiac surgery; and complications of heart failure (ischemic or non-ischemic etiologies):

1) Appropriate analysis and non-clinical testing must validate electromagnetic compatibility (EMC) and electrical safety;
2) Appropriate software verification, validation, and hazard analysis must be performed.
3) The patient contacting components (i.e., catheters) must be demonstrated to be biocompatible;
4) Sterility and shelf life testing must demonstrate the sterility of patient-contacting components and the shelf-life of these components;

5) Non-clinical performance evaluation of the device system (i.e., catheters and pump console) must provide a reasonable assurance of safety and effectiveness for mechanical integrity, durability, and reliability;
6) Labeling must include adequate instructions for use, a detailed summary of the device-related and procedure-related complications pertinent to use of the device, and appropriate warnings and contraindications.

The panel will be asked to discuss the device-related risks to health and the proposed special controls designed to mitigate these risks. Specifically, whether the risks to health as identified in Table 1 are complete and the adequacy of the proposed special controls in mitigating the risks to health for the indications of acute coronary syndrome, cardiac and non-cardiac surgery, complications of heart failure of both ischemic and non-ischemic etiologies are sufficient and/or whether additional or different special controls are recommended.

Reasonable Assurance of Safety and Effectiveness

According to 21 CFR 860.7(d)(1), "There is reasonable assurance that a device is safe when it can be determined, based upon valid scientific evidence, that the probable benefits to health from use of the device for its intended uses and conditions of use, when accompanied by adequate directions and warnings against unsafe use, outweigh any probable risks. The valid scientific evidence used to determine the safety of a device shall adequately demonstrate the absence of unreasonable risk of illness or injury associated use of the device for its intended uses and conditions of use."

According to 21 CFR 860.7(e)(1), "There is reasonable assurance that a device is effective when it can be determined, based upon valid scientific evidence, that in a significant portion of the target population, the use of the device for its intended uses and conditions of use, when accompanied by adequate directions for use and warnings against unsafe use, will provide clinically significant results."

IABP devices have been used widely over the past 40 years. Extensive literature exists which supports the hemodynamic effects and device safety and effectiveness in the device's intended patient population for the specific indications of acute coronary syndrome, cardiac and non-cardiac surgery, complications of heart failure of both ischemic and non-ischemic etiologies . The 2004 ACC/AHA[52] Practice Guidelines for ST Elevation Myocardial Infarction (STEMI) and the 2011 ACC/AHA[53] Percutaneous Coronary Intervention (PCI) Guidelines also support these conclusions. Special Controls have been recommended in Section 8 as a measure to assure that the safety and effectiveness of the device can be appropriately regulated in Class II.

All other intended uses, such as septic shock and intraoperative pulsatile flow generation, require further proof of benefit and we recommend should remain in Class III requiring PMAs. Clinical data demonstrating safety and effectiveness will be needed to demonstrate the utility of the IABP device for all other intended uses.

Consequently, FDA recommends that the classification regulation 21 CFR 870.3535 be

split accordingly based on the proposed Indications of the IABP device to include both a Class II (Special Controls) and Class III (PMA) classification. FDA is not recommending any changes to part (a) (Identification) of the regulation.

21 CRF 870.3535 Intra-aortic balloon and control system

(a) *Identification.* An intra-aortic balloon and control system is a device that consists of an inflatable balloon, which is placed in the aorta to improve cardiovascular functioning during certain life-threatening emergencies, and a control system for regulating the inflation and deflation of the balloon. The control system, which monitors and is synchronized with the electrocardiogram, provides a means for setting the inflation and deflation of the balloon with the cardiac cycle.

(b) *Classification.* (1) Class II (special controls) when the device is indicated for acute coronary syndrome; cardiac and non-cardiac surgery; and complications of heart failure (ischemic or non-ischemic etiologies). The special controls for this device are:

1) Appropriate analysis and non-clinical testing must validate electromagnetic compatibility (EMC) and electrical safety;
2) Appropriate software verification, validation, and hazard analysis must be performed.
3) The device must be demonstrated to be biocompatible;
4) Sterility and shelf life testing must demonstrate the sterility of patient-contacting components and the shelf-life of these components;
5) Non-clinical performance evaluation of the device must provide a reasonable assurance of safety and effectiveness for mechanical integrity, durability, and reliability;
6) Labeling must include a detailed summary of the device-related and procedure-related complications pertinent to use of the device, and appropriate warnings and contraindications.

(2) Class III (premarket approval) for all other intended uses.

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